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Case Report

Case of infantile obesity

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ABSTRACT

Congenital leptin receptor deficiency is a rare autosomal recessive form of monogenic obesity caused by loss-of-function mutations in the leptin receptor function. Due to its subtle signs and symptoms early diagnosis of this becomes a challenge. We report a case of a 7-month-old male child who presented with the complaints of excessive weight gain on exclusive breast feeding with no dysmorphism or developmental delay. Whole exome sequencing helped in diagnosis of leptin receptor deficiency. Specific investigations are needed for diagnosis of genetic forms of obesity. Specific diagnosis helps to prognosticate and counsel parents and help physicians to improve their care in patients with severe early onset obesity.

Keywords: Leptin receptor, Targeted treatment, Infantile obesity

INTRODUCTION

Leptin, produced by adipose tissue, plays a crucial role in maintaining energy homeostasis by signaling the brain to regulate appetite and energy expenditure.[1-7] Leptin receptor deficiency impairs this signaling pathway, leading to severe obesity, hyperphagia, and metabolic dysfunction.[1] This case report contributes to the understanding of mutations of leptin/melanocortin pathway which could change the prognosis of rare severe forms of obesity in a patient presenting with a unique clinical and genetic profile.

CASE REPORT

A 7-month-old male child first born to second degree consanguineous marriage was brought to our hospital by the parents with the complaint of excessive weight gain since 3 months of age associated with hyperphagia. There was no history of dullness of activity, seizures, hypoglycemic episodes or feeding difficulties. Child was diagnosed with hypothyroidism one month back and was on thyroxine at a dose of 50 microgram per day.

The baby was delivered at full term by emergency lower segment caesarean section in view of antepartum hemorrhage with a birth weight of 2.9 kg. child cried immediately after birth and perinatal period was uneventful.

Antenatal targeted imaging for fetal anomalies was found to be normal. Growth scan was abnormal with intra uterine growth restriction of 2 weeks with adequate liquor. Child was on exclusive breast feeding since birth.

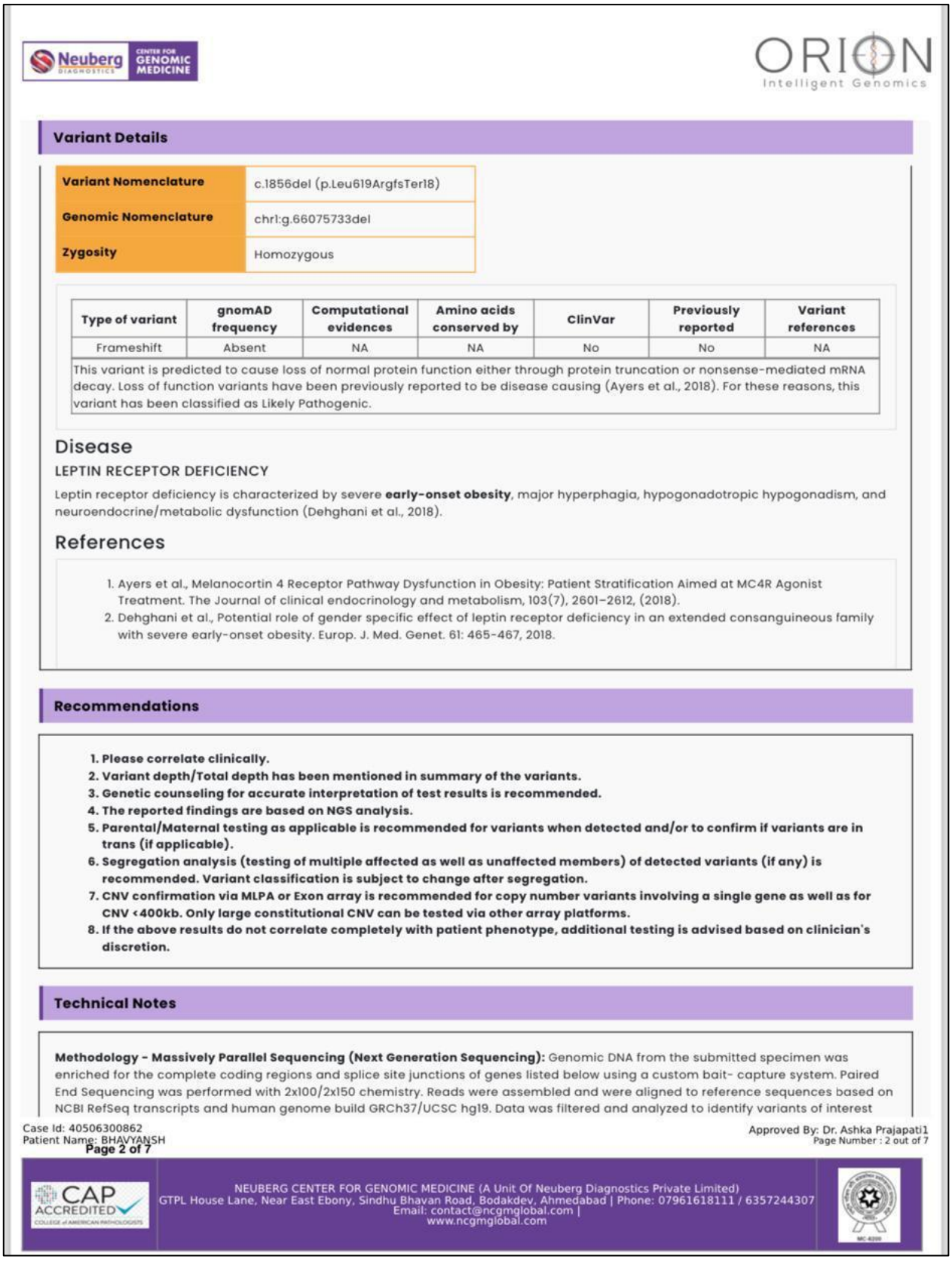
Mother has a history of seizure disorder for 13 years and was on anti-epileptic drugs since last 3 years. she had last seizure episode 1 year 6 months back. She was on phenytoin 100 milligrams twice a day during both pregnancy and lactation.

Child was immunized till date.

On physical examination we noticed short neck, brachydactyly, excessive skin folds in both bilateral upper and lower limbs and normal size of penis with bilateral palpable testis.

Central nervous system examination: did not reveal any abnormality.

Other systems were normal on clinical examination.



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Variant Details

Variant Nomenclature	c.1856del (p.Leu619ArgfsTer18)
Genomic Nomenclature	chr1:g.66075733del
Zygosity	Homozygous

Type of variant	gnomAD frequency	Computational evidences	Amino acids conserved by	ClinVar	Previously reported	Variant references
Frameshift	Absent	NA	NA	No	No	NA

This variant is predicted to cause loss of normal protein function either through protein truncation or nonsense-mediated mRNA decay. Loss of function variants have been previously reported to be disease causing (Ayers et al., 2018). For these reasons, this variant has been classified as Likely Pathogenic.

Disease

LEPTIN RECEPTOR DEFICIENCY

Leptin receptor deficiency is characterized by severe **early-onset obesity**, major hyperphagia, hypogonadotropic hypogonadism, and neuroendocrine/metabolic dysfunction (Dehghani et al., 2018).

References

1. Ayers et al., Melanocortin 4 Receptor Pathway Dysfunction in Obesity: Patient Stratification Aimed at MC4R Agonist Treatment. The Journal of clinical endocrinology and metabolism, 103(7), 2601–2612, (2018).
2. Dehghani et al., Potential role of gender specific effect of leptin receptor deficiency in an extended consanguineous family with severe early-onset obesity. Europ. J. Med. Genet. 61: 465-467, 2018.

Recommendations

1. **Please correlate clinically.**
2. **Variant depth/Total depth has been mentioned in summary of the variants.**
3. **Genetic counseling for accurate interpretation of test results is recommended.**
4. **The reported findings are based on NGS analysis.**
5. **Parental/Maternal testing as applicable is recommended for variants when detected and/or to confirm if variants are in trans (if applicable).**
6. **Segregation analysis (testing of multiple affected as well as unaffected members) of detected variants (if any) is recommended. Variant classification is subject to change after segregation.**
7. **CNV confirmation via MLPA or Exon array is recommended for copy number variants involving a single gene as well as for CNV <400kb. Only large constitutional CNV can be tested via other array platforms.**
8. **If the above results do not correlate completely with patient phenotype, additional testing is advised based on clinician's discretion.**

Technical Notes

Methodology - Massively Parallel Sequencing (Next Generation Sequencing): Genomic DNA from the submitted specimen was enriched for the complete coding regions and splice site junctions of genes listed below using a custom bait- capture system. Paired End Sequencing was performed with 2x100/2x150 chemistry. Reads were assembled and were aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. Data was filtered and analyzed to identify variants of interest

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Patient Name: BHAVYANSH
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Figure 1: Clinical report.

Anthropometry

Anthropometry of patients showed in Table 1.

Table 1: Head circumference.

Variables	Observed	Expected	Percentile (%)
Height (cm)	70	69	+0.17SD, 56.6
Weight (kg)	16	11.5	+6.8SD, >99.9
HC (cm)	45	43	+0.68SD, 75.1

Investigations

Investigations were as-Hb-9.2 g/dL, IGF1 was normal, TSH: 12.6 (elevated), free T4 : normal, HBA1C: 6.0, RBS: 126 mg/dl, total cholesterol: 184 mg/dl, HDL: 43 mg/dl (low), LDL: 94 mg/dl (low), triglycerides: 236 mg/dl (elevated), VLDL: 47 mg/dl (elevated), Sr insulin: 11.37 mU/L, Sr cortisol : 10.96, Sr calcium 10.1 and Sr PTH : 41.4 pg/ml.

2D ECHO: Structurally normal heart.

USG abdomen: Mild prominent liver with normal echotexture.

MRI brain: Normal sized pituitary gland with no obvious lesions.

Whole exome sequencing: Autosomal recessive leptin receptor deficiency.

DISCUSSION

The leptin hormone has effects on hunger and energy use by regulating adipose tissue mass through hypothalamus. The hormone acts through leptin receptor which interacts with gangliosides and regulate the energy metabolism and body weight. Variation in leptin receptor have been associated with obesity and increased susceptibility to infections due to its partial effect on immune function.[8] This rare endocrine disorder is estimated to affect 1.34 per 1 million people all over the world.[11]

In our case 7 month old male child was bought with excessive weight gain. Dietary history was analysed and nutritional cause of obesity was ruled out. All the blood investigations and imaging done were not conclusive of the cause of the early onset obesity like the other causes mentioned in previous study.[12] To rule out genetic causes of obesity whole exome sequencing was done which revealed congenital leptin receptor deficiency. Parents were advised about dietary management by the paediatric endocrinologist who also counselled about the nature of the disease, impact on development and advised genetic counselling before planning second pregnancy.[10] This case report underscores the significance of diagnosing a rare genetic obesity disorder within a family.[9] It also emphasis the crucial role of genetic testing for patients suspected of having a genetic obesity condition, as it can pave the way for personalized treatment approaches, including guidance from specialized healthcare providers, informed caregivers and potentially targeted pharmacotherapy.[9]

CONCLUSION

Diagnosis of this rare genetic obesity has a deep impact on the life of the child and the family. Congenital leptin receptor deficiency should be considered in the differential diagnosis in any child with hyperphagia and severe obesity in the absence of dysmorphism or developmental delay. Parents perception need to be understood and extensively counselled about the nature of disease and outcome.

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